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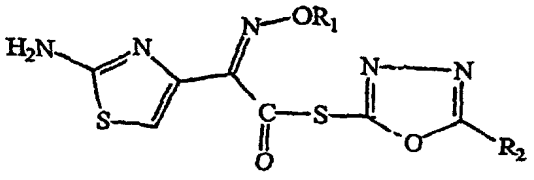
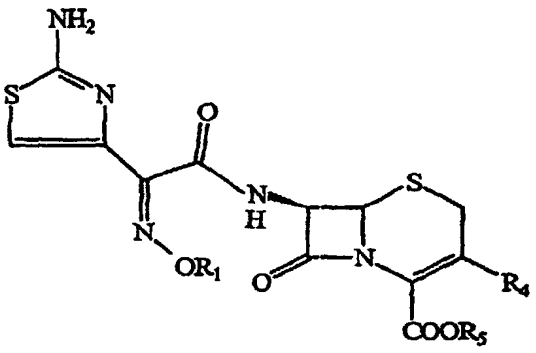
(54) Title: NOVEL THIOESTER DERIVATIVES OF THIAZOLYL ACETIC ACID AND THEIR USE IN THE PREPARATION OF CEPHALOSPORIN COMPOUNDS



(I)



(II)

(57) Abstract: The present invention provides novel thioester derivatives of thiazolyl acetic acid of the general formula (I), also, the invention provides a method for preparation of the thioester derivatives and reaction of the thioester derivatives with cephem carboxylic acids to produce cephalosporin antibiotic compounds having general formula (II).

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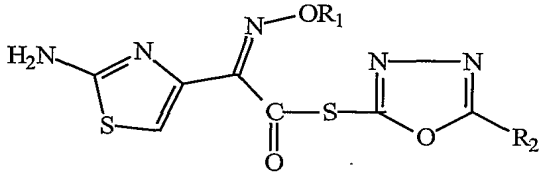
NOVEL THIOESTER DERIVATIVES OF THIAZOLYL ACETIC ACID AND THEIR USE IN THE PREPARATION OF CEPHALOSPORIN COMPOUNDS

Technical Field

The present invention relates to novel thioester derivatives of thiazolyl acetic acid of the general formula **(I)**. The invention also relates to a novel process for preparation of the thioester derivatives. The reactive thioester derivatives are useful as intermediate for the preparation of cephalosporin antibiotics having the formula **(II)**. In addition, the present invention also relates to a process for preparation of cephalosporin antibiotics using the said thioester derivatives.



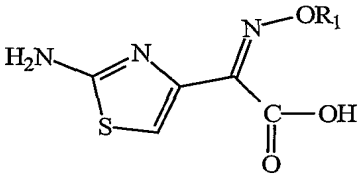
(I)

wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$
(R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl).

R_2 represents C_1 - C_4 alkyl or phenyl

Background Art

Acid chlorides, anhydrides, esters, amide etc. are reported in the chemical literature for activation of carboxylic acid of formula **(IV)**. Activation in the form of acid chloride required protection and deprotection of NH_2 group.



(IV)

Activation of acid **(IV)** is reported by SO_2Cl_2/DMF in US patent 5,856,502 and $SOCl_2$/DMF in US patent 5,037,988. These processes suffer the limitation of using harmful and pungent smelling chemicals like $SOCl_2$, SO_2Cl_2 along with solvents like benzene, toluene, etc. and stringent conditions required for carrying out the reactions at commercial scale.

In US patent No.4,576,749 and 4,548,748 the acid of formula **(IV)** have also been activated by reacting with 1-hydroxybenzotriazole (HOBT) or 2-mercaptobenzothiazole (MBT) in the presence of dicyclohexylcarbodiimide (DCC) to produce reactive ester of the acid **(IV)** which

then reacted to cephem moiety to prepare cephem antibiotics, but the processes are time consuming and with low yields, hence not suitable.

US patent 4767852 discloses a process for production of cephems by acylating 7-amino-3-cephem-4-carboxylic acid with 2-mercaptobenzothiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetate (MAEM). Similarly, US Pat.No.5026843 (1991) disclosed a process for preparing ceftriaxone disodium hemiheptahydrate by acylation of ACT by using MAEM as acylating agents in good yield and quality. Thus MAEM has become the standard acylating agent for the preparation of cephalosporins having an oximino group and a 2-aminothiazolyl group in 7-position of cephem compounds.

However, the synthesis of MAEM from acid **(III)** and 2,2'-dithio-bis-benzothiazole involves use of costly condensing agent triphenylphosphine (TPP). Moreover, during condensation of MAEM with 7-amino-3-cephem-4-carboxylic acid compound **(III)**, a toxic compound MBT is also produced as a byproduct, see e.g., Chemical Abstracts, 111, 19243p (1989) which is difficult to remove completely.

Thus it is evident that the procedures described in the prior art for preparation of these antibiotics are complex, involving protection, deprotection and are associated with toxic byproduct generation. Hence there is a need to develop new acylating agents which are capable of transferring the 2-aminothiazolyl moiety to cephem compounds of formula **(III)** in good yield but without producing this toxic byproduct. On the similar lines, a new thioester was reported by D.G.Walker, Tet. Lett. 1990, 31,6481 to acylate the cephem moiety to get cefepime sulfate but yields obtained by using this thioester were in the range of 54-73% which cannot be considered as good yield to operate a process at commercial scale. The use of this thioester was reported in the Tet. Lett. 1990, 31, 6481 only for cefepime and not for other cephalosporins. This thioester was exploited in US patent No. 5869649 for making three other important cephem antibiotics.

Disclosure of the Invention

The primary objective of the invention is to prepare novel thioester derivatives of thiazolyl acetic acid of the general formula **(I)**, which would be better than the existing reactive derivatives and suitable for being used in the manufacture of cephalosporin antibiotics.

Another objective of the present invention is to provide a process for the synthesis of thioester derivatives of formula **(I)** from thiazolyl acetic acid of the general formula **(IV)** and thio-oxadiazoles of the general formula **(VI)**.

Yet another objective of the present invention is to provide a simple, high yielding and cost-effective process for the preparation of cephalosporin antibiotics of the general formula **(II)**.

Still another objective of the present invention is to produce cephalosporin antibiotics that are highly pure and free from toxic byproducts.

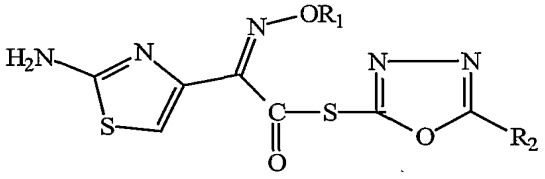
One more objective of the present invention is to provide a process for the preparation of cephalosporin antibiotics of the general formula **(II)** from the said novel thioester derivatives.

Summary of the Invention

The present invention provides novel thioester derivatives of thiazolyl acetic acid of the general formula **(I)**. The invention also provides a method by which the said thioester derivatives can be prepared. The thioester derivatives so obtained are reacted with 7-amino-cephem carboxylic acids of the general formula **(III)** to produce cephalosporin antibiotic compounds having the general formula **(II)**.

Detailed Description of the Invention

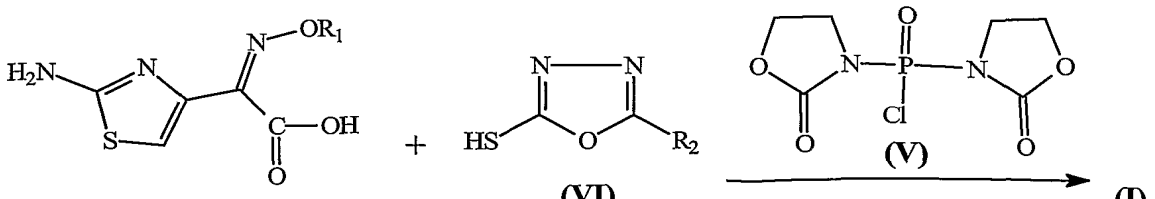
The present invention provides new thioesters of the general formula **(I)** that are prepared by a novel method which has not been reported in the prior art. The use of these compounds in the process for preparing cephem derivatives renders the process entirely new and different from others. The novel derivative of thiazolyl acetic acid is represented by the formula **(I)**



(I)

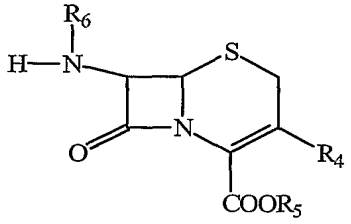
wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl).
R_2 represents C_1 - C_4 alkyl or phenyl

The synthesis of compound **(I)** is achieved by reacting thiazolyl acetic acid of the general formula **(IV)** with thio-oxadiazoles of the general formula **(VI)** in organic solvent in presence of an organic base. The condensation is done with the help of a condensation agent of the formula **(V)**. When the above reaction is carried out, the temperature is maintained between -10^0 and +30^0C.



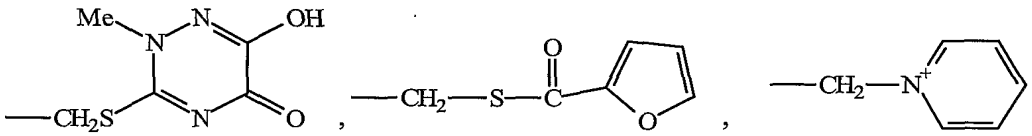
(IV) **(VI)** **(V)** **(I)**

wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and
R_3 represents H or C_1-C_7 alkyl).
R_2 represents C_1-C_4 alkyl or phenyl



(III)

wherein R_4 is CH_3, -CH=CH_2, CH_2OCH_3, CH_2OCOCH_3,



or a standard cephalosporin substituent.

R_5 is hydrogen, salt or carboxylic protecting group.
R_6 is hydrogen or silyl.

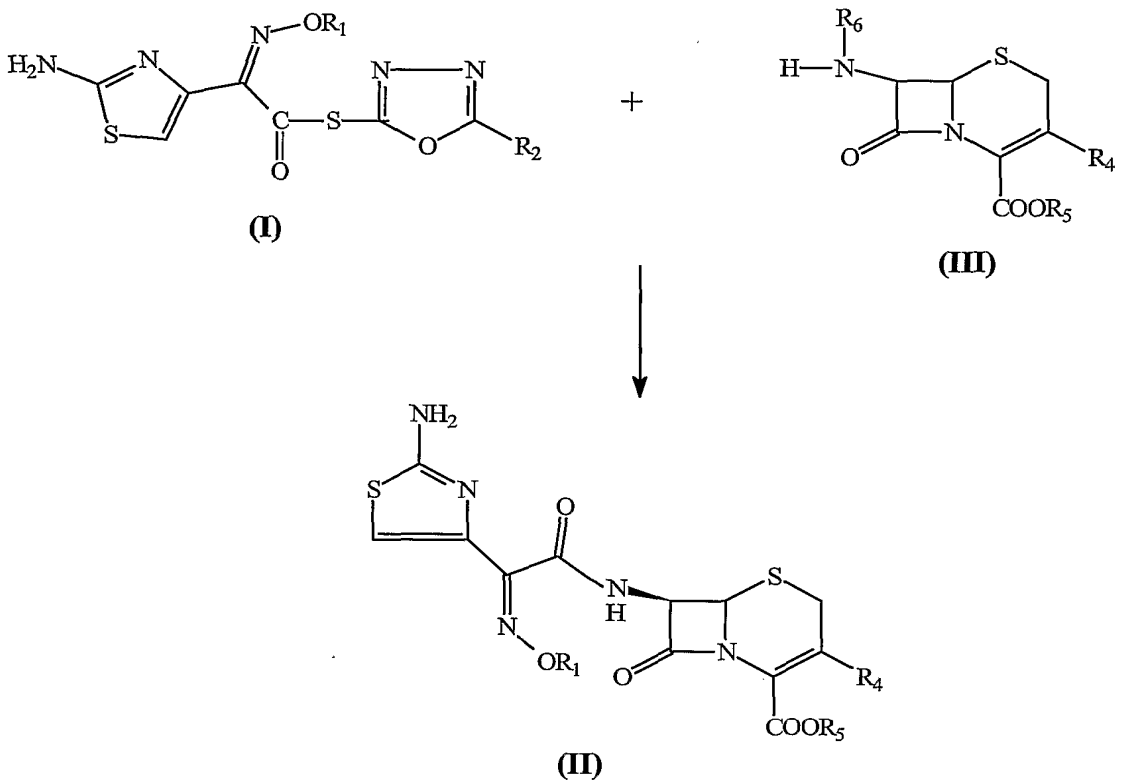
In an embodiment the organic solvent is selected from the group comprising dichloromethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, acetone, carbon tetrachloride and mixtures thereof.

In another embodiment the condensation agent is bis-(2-oxo-oxazolidinyl) phosphinic chloride.

In still another embodiment the organic base is selected from triethylamine, diethylamine, tributylamine, pyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, N-methylmorpholine and mixtures thereof.

The compound **(I)** so obtained is reacted with 7-amino cephem carboxylic acids of the general formula **(III)** in organic solvent in presence of organic base to obtain cephalosporin antibiotics of general formula **(II)**.

For protection of carboxylic group as ester, following group can be used which are easily converted into free carboxylic acid, e.g. p-methoxybenzyl, p-nitrobenzyl, diphenyl methyl, phenacyl trimethylsilyl.



(I) (III) (II)

wherein, R_1, R_2 R_4, R_5, & R_6 are as defined above.

The present invention provides a method by which cephalosporin antibiotics are obtained in high purity (95-99%) and excellent yield (79-95%) without the necessity for protecting the amino group of the acylating agents and the production of toxic byproduct namely 2-mercaptobenzothiazole is avoided.

The substituent R_4 in cephem compound **(III)** represents methyl, acetyloxymethyl, methoxymethyl, vinyl, pyridylmethyl, propenyl, 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazine-3-thiol, furanyl-2-carbonyl thiol or a standard cephalosporin substituents defined by R_4. In general, R_4 represents $-CH_2-X$ wherein X is a residue of any organic or inorganic nucleophilic compound, e.g., halogen, hydroxy, cyano, mercapto, azido, amino, etc. Furthermore, X may preferably represent residue of any 5 or 6 membered heterocyclic thiol. The heterocyclic thiol contains one to four hetero atoms selected from a group of nitrogen, oxygen and/or sulfur. Some of the examples of five membered ring are 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1H-tetrazolyl, 1,2,4-tetrazolyl, 1,2,3-tetrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, etc. The six membered heterocyclic ring can be exemplified by pyridyl, pyrimidyl, pyridinyl-N-oxide, etc.

R_5 represents hydrogen, salt or a standard carboxylic protecting group.

R_6 is hydrogen or silyl.

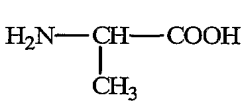
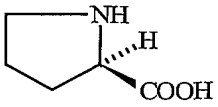
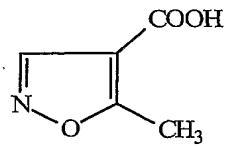
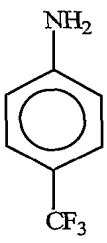
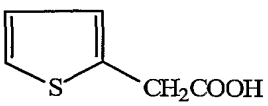
The condensation of cephem compound **(III)** with thioester **(I)** is performed by two different methodologies (a) by acylating the compound **(III)** (when R_6 is H) with compound **(I)** in aqueous organic solvent; (b) by acylating compound **(III)** (when R_6 is silyl) with compound **(I)** in aprotic organic solvents. Both the approaches are comparable and afforded excellent yields and purities of cephem antibiotics **(II)**.

Acylation of compounds of formula **(III)** (when R_6 is H) is performed in presence of a water miscible solvent like tetrahydrofuran (THF), acetonitrile, acetone, dioxane, N,N-dimethylformamide etc. but the preferable solvents are THF and acetonitrile.

In an embodiment of the present invention, acylation of compound of formula **(III)** (when R_6 is silyl) is carried out in aprotic organic solvents like halogenated hydrocarbons, toluene, alkyl ethers etc., but the preferred solvent is dichloromethane. Suitable silylating agents used for the reaction are hexamethyldisalazane, bis(trimethyl)silylacetamide and trimethylsilyl chloride.

In another embodiment of the present invention, the organic base may be selected from triethylamine, diethylamine, tributylamine, N-alkylpyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, N-methylmorpholine, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylamino pyridine and mixtures thereof.

The utility of the novel thioesters of 2-mercapto-5-phenyl-1,3,4-oxadiazole was tried in various coupling reactions of carboxylic acids and amines. Most of amide formation reactions have shown good results. L-alanine, 5-methylisoxazole-4-carboxylic acid, 2-thienylacetic acid, etc. are some of the compounds, which have been activated by above mentioned thiol. Few results are summarized in the following table.

S.No.	Acids	Amines	% by HPLC
1.			70 - 88%
2.			90 - 97%
3.		7-Aminocephalosporanic acid	80 - 90%

In an embodiment, R_4 represents any of methyl, vinyl, methoxymethyl, pyridylmethyl, acetyloxymethyl, (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl) thiomethyl, furylcarbonyl thiomethyl or a standard cephalosporin substituent.

In another embodiment, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl).

In still another embodiment, R_5 is hydrogen or alkali metal salt.

In yet another embodiment, the alkali metal salts are selected from sodium, potassium and lithium salts.

In another embodiment, the compound of formula II is a syn isomer.

In still another embodiment, R_6 is silyl, the acylation is achieved by doing the reaction in aprotic organic solvent like halogenated hydrocarbon, toluene, alkyl ether preferably in dichloromethane.

In another embodiment, R_2 is methyl and R_4 represents any of (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, and purification of this compound is achieved by dissolving the crude product in mixture of water and water miscible organic solvent selected from acetone, IPA, dioxane and mixture thereof.

In another embodiment, the organic base is selected from the group consisting of triethylamine, N-methylmorpholine, N-methylpyridines, N-methylanilines, 1,5-diazabicyclo[4.3.0] non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylaminopyridine, and mixtures thereof.

In an embodiment, R_2 is methyl, R_4 is (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, the colour impurities are separated at -10^{0}C to 0^{0}C and precipitation by water miscible organic solvent selected from acetone, IPA, dioxane and mixture thereof.

Thus the present invention provides novel thioester derivatives of thiazolyl acetic acid of the general formula **(I)**, also, the invention provides a method by which the said thioester derivatives can be prepared by reacting thiazolyl acetic acid of the general formula **(IV)** with 2-mercapto-5-substituted-1,3,4-oxadiazole of the general formula **(VI)** (preparation of VI, J. Am. Chem. Soc., 1955, 77, 400) in a solvent, in presence of an organic base and with the help of condensation agent bis- (2-oxo-oxazolidinyl) phosphinic chloride of the formula **(V)** (preparation of V, Synthesis, 1980, 547). The so obtained thioester derivatives are reacted with 7-amino-cephem carboxylic acids of the general formula **(III)** to produce cephalosporin antibiotic compounds having the general formula **(II)**. The cephalosporin antibiotics so obtained are of high purity (95-99%). The method gives an excellent yield (79-95%) of

cephalosporin without necessitating for the protection of the amino group of the acylating agents, and the toxic byproduct 2-mercaptobenzothiazole is not produced.

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure. However, since the major characteristic feature of the present invention resides in the use of novel reactive thioester derivatives of thiazolyl acetic acid of the general formula **(I)** in preparing the cephalosporin antibiotics, the technical scope of the present invention should not be limited to the following examples.

The following examples are provided to illustrate but not to limit the claimed invention.

EXAMPLES

Example - I

Synthesis of 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (I).

(Z)-(2-aminothiazol-4-yl)methoxyimino acetic acid (20.1g), triethylamine (22.2g) were suspended in dry dichloromethane (150ml), and then bis-(2-oxo-oxazodinyl)phosphinic chloride (25.4g) was added in one lot at 0-5^{0}C and stirred for 1 hr. The 2-mercapto-5-phenyl-1,3,4-oxadiazole (21.3g) was added at 0-5^{0}C. The reaction mixture was stirred for 3-4 hours. After the reaction was complete, distilled water 100ml was added to the reaction solution and the mixture was stirred for 10 min. The organic layer was separated and washed successively with 2% aq. solution bicarbonate solution (100 x 2ml) and saturated saline (100ml), dried over sodium sulphate, filtered and then concentrated under reduced pressure. To the residue, IPE (isopropyl ether) (300ml) was added and solid was filtered, washed with IPE (100ml). Dried to obtain 30.6g (yield 85%) of the title compound as light yellow solid.

Melting point : 109 - 110^{0}C

^{1}HNMR (DMSO-d_6) : δ3.90 (3H,s,N-OCH_3), 7.11(1H,s, thiazole ring proton), 7.29(2H,bs,NH_2), 7.6-7.9(5H, m, - C_6H_5)

^{13}C-NMR (Acctone-d_6) : δ 63.16, 108.7, 122.1, 129.7, 132.6, 133.7, 141.6, 146.75, 159.3, 159.6, 169.7, 173.1.

Example - II

Synthesis of 2-mercapto-5-methyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate.

(Z)-(2-Aminothiazol-4-yl)methoxyimino acetic acid (20.1g), triethylamine (22.2g) were suspended in dry dichloromethane (150ml), and then bis-(2-oxo-oxazodinyl)phosphinic chloride (25.4g) was added in one lot at 0-5^{0}C and stirred for 1 hr. The 2-mercapto-5-methyl-

1,3,4-oxadiazole (13.0g) was added at 0-5^{0}C. The reaction mixture was stirred for 3-4 hours and worked up in the same way as described in example-I to obtain 25.8g (yield 84%) of the title compound as light yellow solid.

Melting point : 80 - 81^{0}C
^{1}HNMR (DMSO-d_6) : δ2.42(3H,s,CH_3), 3.8(3H,s,OCH_3), 7.06(1H,s,thiazole ring), 7.3(2H,bs,NH_2)
^{13}C-NMR (DMSO-d_6): δ 11.8, 67.9, 109.0, 141.0, 146.9, 160.0, 161.5, 169.8, 173.7.

Example - III

Synthesis of 2-mercapto-5-methyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-(methoxycarbonyl)-methoxyimino acetate.

(Z)-2-(2-aminothiazol-4-yl)-(methoxycarbonyl) methoxyimino acetic acid (3.88g) was suspended in dichloromethane (40ml), TEA (triethylamine) (3.33g) was added at 0^0 - 10^{0}C followed by addition of bis-(2-oxo-oxazolidinyl)phosphinic chloride (3.81g). The mixture was stirred for 1 hr. and 2-mercapto-5-phenyl-1,3,4-oxadiazole (2.6g) was added. The reaction was monitored by HPLC. After completion of reaction, it was worked up as described in example I, to obtain 4.5g (72%) title compound as yellow solid.

Melting point : 115 - 117^{0}C
^{1}H-NMR : δ3.61(3H,s,-$COOCH_3$), 4.79(2H,s,-OCH_2-CO), 7.14(1H,s,thiazole H), 7.34(2H,bs,NH_2), 7.6-7.9 (5H,m,-C_6H_5)
^{13}C-NMR : δ 52.6, 72.1, 109.9, 111.1, 127.4, 129.8, 133.8, 141.1, 147.7, 159.3, 159.9, 169.4, 166.7.

Example - IV

7-[[(Z)-2-(2-Aminothiazol-4-yl)2-methoxyimino]acetamido]-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylicacid disodium hemiheptahydrate (Ceftriaxone sodium).

7-Amino-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3yl)thio]methyl]3-cephem-4-carboxylic acid (20.0g) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl) 2-methoxyiminoacetate (23.3g) were suspended in a mixture of THF (180ml), H_2O (80ml) and DMAc (dimethyl acetamide) (30ml) maintained at 0^0 - 1^{0}C under stirring. Triethylamine (11.9ml) was added in 2-3 hours at 5^{0}C maintaining the pH 7.5 - 8.5. The reaction progress was monitored by HPLC. After the reaction was complete, the mixture was extracted with dichloromethane (3 x 100ml). The aq. layer was separated and treated with charcoal (0.2g). A solution of sodium-2-ethylhexanoate (30.5g) in acetone was added to

filtrate at 10-15^{0}C and stirred for 1.5 hours (400ml) of acetone was added in 1 hour at 10-15^{0}C to complete the crystallization. The product was filtered under N_2 atmosphere and wet cake was dissolved in mixture of water and acetone (1:2), and cooled to -10^{0}C. Coloured impurities were separated. The solution was decanted and diluted with acetone (600ml) at 18-20^{0}C. Precipitated solid was filtered under N_2 and washed with acetone (20ml). Dried under vacuum at 40-45^{0}C to get pure Ceftriaxone sodium, 28.5g (yield 89%).

HPLC (purity): 99.0%

Example - V

7-[[(Z)-2-(2-Aminothiazol-4-yl)2-methoxyimino]acetamido]-3-[[(2,5-dihydro-6-hydroxy-2-ethyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylicacid disodium hemiheptahydrate (Ceftriaxone sodium).

7-Amino-3-[[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3yl)thio]methyl]3-cephem-4-carboxylic acid (20.0g) was suspended in dichloromethane (200ml). To this was added hexamethyldisilazane (15.0g) and trimethylsilyl chloride (3.0g). The suspension was refluxed for 2-3 hours to get clear solution. Cooled to 0^{0}C and triethylamine (13.6g) was added slowly. At the same temperature, 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl) 2-methoxyiminoacetate (23.3g) was added. The reaction mixture was monitored by HPLC. After completion of reaction, 200ml water was added and pH was adjusted to 7.0. The aqueous layer was separated, charcoalized and treated with sodium-2-ethylhexanoate (30.5g) in acetone, reaction was proceeded by same method as mentioned in Ex-IV to get crude ceftriaxone sodium (25.0g)

Example - VI

3-Acetyloxymethyl-7-[(Z)-(2-aminothiazolyl-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylic acid (Cefotaxime acid).

A mixture of THF (250ml) and water (150ml) and N,N-dimethylacetamide (25.0ml) was stirred under inert atmosphere. At 0^0 - 1^{0}C, 7-aminocephalosporanic acid (25.0g) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)2-methoxyimino acetate (39.8g) were added. Triethylamine (20.4g) was slowly added to reaction by maintaining pH 7.5 to 8.5. The reaction was followed by HPLC. After 4-5 hrs., the reaction mixture was extracted by methylene chloride. The aqueous layer is subjected for charcoal (0.125g) treatment. Ethylacetate was added to the filtrate and the solution was acidified with dil. HCl at 10^{0}C to pH 3.0. The solid separated was filtered, washed with water and ethylacetate and then dried under vacuum at 40-45^{0}C to get Cefotaxime, 40.9g (yield 98%).

HPLC (purity)= 98 - 99%

Example - VII

3-Acetyloxymethyl-7-[(Z)-(2-aminothiazolyl-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylic acid (Cefotaxime acid).

7-Aminocephalosporanic acid (25.0g) was taken in dichloromethane (200ml). Hexamethyldisilazane (14.7g) and trimethylsilyl chloride (5.1g) were added to it and slurry was refluxed till a clear solution is obtained. The clear solution was cooled to 0^0C and triethylamine (13.9g) was added to it. At 0^0C, 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (39.0g) was added, reaction was monitored by HPLC. After 4-5 hrs., HPLC showed disappearance of 7-amino cephalosporanic acid. Water (200ml) was added to reaction mixture and pH of mixture was adjusted by triethylamine to 7.0 - 7.5. The aq. layer was separated and treated with charcoal. Ethylacetate was added to aq. layer and pH was adjusted to 3.0 at 10^0C. The solid was filtered and washed with water and ethylacetate. Dried under vacuum at 40^0C to get 36.0g of cefotaxime acid.

HPLC (purity)= 97 - 98%

Example - VIII

7-[[(Z)-2-(Aminothiazol-4-yl)-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid [Cefixime].

A mixture of THF (200ml) and water (200ml) was stirred at 0-1^0C under inert atmosphere, 7-amino-3-vinyl-3-cephem-4-carboxylic acid (21.4g) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-[2-(aminothiazol-4-yl)methoxycarbonyl methoxyimino] acetate (46.0g) were added. Triethylamine (15.1g) was added slowly and reaction mixture was stirred at 0-5^0C maintaining at pH 7.5 to 8.5. The reaction was monitored by HPLC, after completion of reaction, it was worked up as described in example (V). The wet product is taken in water and treated with aq. sodium hydroxide (7.19g) solution at 0-2^0C. After 10 min., pH was lowered to 7.0 by addition of acetic acid.

The solution was treated with charcoal, filtered and acidified with 1N HCl. Solid precipitated was filtered, washed with water and dried under vacuum to give Cefixime, 36.2 g (yield 80%).

HPLC (Purity) : 99.5%

Example - IX

7-[[(Z)-2-(Aminothiazol-4-yl)-2-methoxyimino]acetamido]-3-methyl-3-cephem-4-carboxylic acid [Cefetamet].

7-Aminodiacetyloxy cephalosporanic acid (2.14g), active ester, 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (3.97g) were suspended in mixture of THF (tetrahydrofuran) (20ml) and water (20ml). TEA was added slowly. The reaction was proceeded in same way as described in example to obtain Cefetamet, 3.65g (yield 92%).

HPLC (purity) : 99.0%

Example - X

7-[[(Z)-2-(Aminothiazol-4-yl)-2-methoxyimino]acetamino]-3-methoxymethyl-3-cephem-4-carboxylic acid [Cefpodoxime acid].

7-Amino-3-methoxymethyl-3-cephem-4-carboxylic acid (24.2g) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (39.7g) were suspended in 400ml of THF and water mixture (1:1). At 10^0C TEA added to maintain pH 7-8. The reaction was monitored and proceeded as described in example IV. To the separated aq. layer, pH was adjusted to 2.7 using 16-18% sulphuric acid. Solid was cooled to 10^0C, filtered and washed with water (3x50ml) and finally with acetone (20ml) to obtain the Cefpodoxime acid, 37.5g (yield 88%).

HPLC (purity) : 98.0%

Example - XI

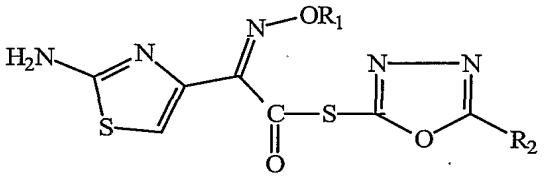
7-[[(Z)-2-(Aminothiazol-4-yl)-2-methoxyimino]acetamido]-3-(furanylcarbonyl) thiomethy]-3-cephem-4-carboxylic acid (Ceftiofur).

7-Amino-3-[(2-furanylcarboxyl)thiomethy]-3-cephem-4-carboxylic acid (3.4g) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (4.0g) were added to a mixture of THF (35ml) and water (35ml) at temperature 5^0C. The pH of reaction was maintained at 7.5 to 8.5 by addition of TEA during the reaction. After completion of reaction, the reaction was extracted with methylene chloride (25ml x 3). The aqueous layer was diluted with 15ml THF and pH was lowered to 3 by addition of 1N HCl. The solution is saturated by salt. The organic layer was separated and pH was further adjusted to 0.5 by concentrated HCl. IPE (250ml) was added to precipitate the hydrochloride salt of Ceftiofur, 4.43g (yield 79.0%).

HPLC (purity) : 98.0%

CLAIMS

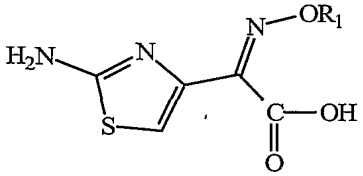
1. A novel derivative of thiazolyl acetic acid represented by the formula **(I)**



(I)

wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl).
R_2 represents C_1 - C_4 alkyl or phenyl

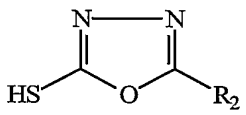
2. A process for preparing thiazolylacetic acid derivative represented by formula **(I)**, said process comprises the step of reacting a thiazolylacetic acid represented by formula **(IV)**



(IV)

wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl).

with thio-oxadiazole of formula **(VI)** in presence of an organic solvent base and a



(VI)

wherein, R_2 represents C_1 - C_4 alkyl or phenyl

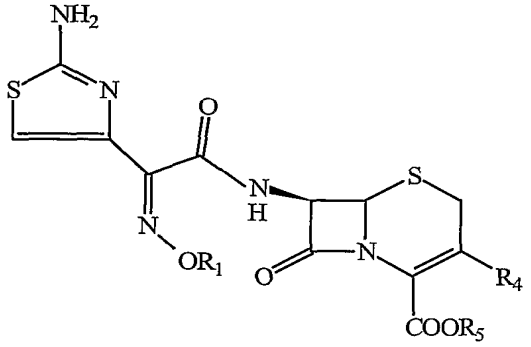
condensation agent at temperature being maintained in the range -10^0C to $+30^0$C.

3. The process of claim 2 wherein the organic solvent is selected from the group comprising dichloromethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, acetone, carbon tetrachloride and mixture thereof.

4. The process of claim 2 wherein the organic base is selected from the group comprising triethylamine, diethylamine, tributylamine, pyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, N-methylmorpholine and mixtures thereof.

5. The process of claim 2 wherein the condensation agent selected is bis-(2-oxo-oxazolidinyl)phosphinic chloride.

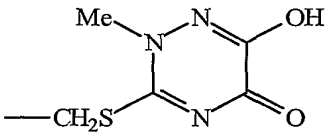
6. A process for preparing a compound of formula **(II)**



(II)

wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl).

R_4 is CH_3, -CH=CH_2, CH_2OCH_3, CH_2OCOCH_3,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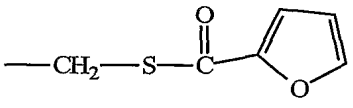
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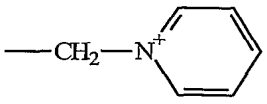
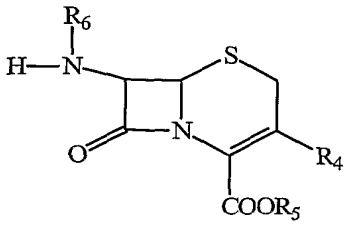


or a standard cephalosporins substituent.

R_5 is H or a salt or a carboxylic protecting group.
R_6 is H or silyl

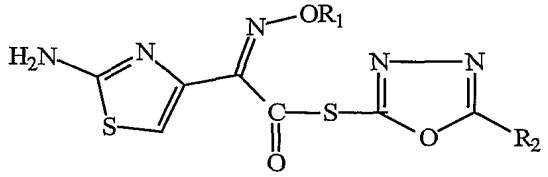
acylating a compound of formula **(III)**



(III)

wherein, R_4, R_5 and R_6 are defined as above

with a compound of formula I. In the presence of an organic solvent, organic base and a silylating agent at a temperature in the range of –10°C to +30°C



(I)

wherein, R_1 & R_2 are as defined above.

7. The process of claim 6 wherein R_5 is hydrogen or alkali metal salt.

8. The process of claim 6 wherein said compound of formula II is a syn isomer.

9. The process of claim 6 wherein R_6 is H, the acylation is done in the presence of water and an organic solvent selected from the group consisting of tetrahydrofuran, N,N-dimethylacetamide, N,N-dimethylformamide, dioxane, and mixtures thereof.

10. The process of claim 6 wherein R_6 is silyl, the acylation is achieved by doing the reaction in aprotic organic solvent like halogenated hydrocarbon, toluene, alkyl ether preferably in dichloromethane.

11. The process of claim 6 wherein the organic base is selected from the group consisting of triethylamine, N-methylmorpholine, N-methylpyridines, N-methylanilines, 1,5-diazabicyclo[4.3.0] non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylaminopyridine, and mixtures thereof.

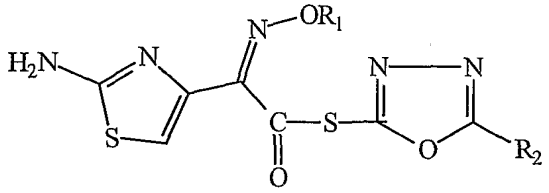
12. The process of claim 6 wherein R_2 is methyl, R_4 is (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, purification of this compound is achieved by dissolving the crude product in mixture of water and water miscible organic solvent selected from acetone, IPA, dioxane and mixture thereof.

13. The process of claim 6 wherein R_2 is methyl, R_4 is (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, the colour impurities are separated at -10^{0}C to 0^{0}C and precipitation by water miscible organic solvent selected from acetone, IPA, dioxane and mixture thereof.

AMENDED CLAIMS

[received by the International Bureau on 06 May 2002 (06.05.02);
original claims 1-6,8,9,11-13 amended; remaining claims unchanged (3 pages)]

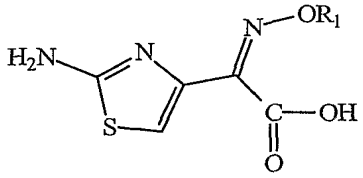
1. A novel derivative of thiazolyl acetic acid represented by the formula **(I)**



(I)

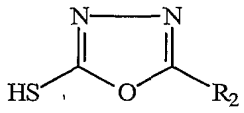
wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl).
R_2 represents C_1 - C_4 alkyl or phenyl

2. A process for preparing thiazolylacetic acid derivative represented by formula **(I)**, said process comprises the step of reacting a thiazolylacetic acid represented by formula **(IV)**



(IV)

wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl).
with a substituted oxadiazole-2-thiol of formula **(VI)**



(VI)

wherein, R_2 represents C_1 - C_4 alkyl or phenyl

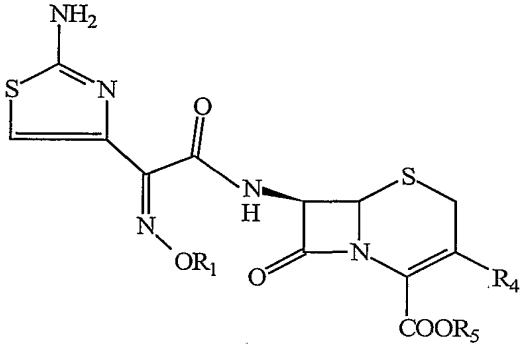
in presence of an organic solvent, an organic base and a condensation agent at a temperature being maintained in the range -10^0C to $+30^0$C.

3. The process of claim 2 wherein the organic solvent is selected from the group comprising dichloromethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, acetone, carbon tetrachloride or mixtures thereof.

4. The process of claim 2 wherein the organic base is selected from the group comprising triethylamine, diethylamine, tributylamine, pyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, N-methylmorpholine or mixtures thereof.

5. The process of claim 2 wherein the condensing agent is bis-(2-oxo-oxazolidinyl)phosphinic chloride.

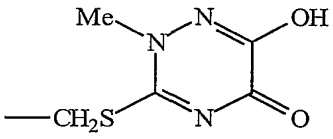
6. A process for preparing a compound of formula **(II)**

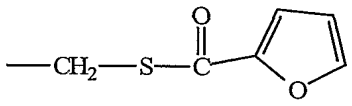


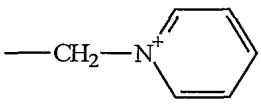
(II)

wherein, R_1 represents H, trityl, CH_3, $CR_aR_bCOOR_3$ (R_a and R_b independently of one another represents hydrogen or methyl and R_3 represents H or C_1-C_7 alkyl);

R_4 is CH_3, -CH=CH_2, CH_2OCH_3, CH_2OCOCH_3,



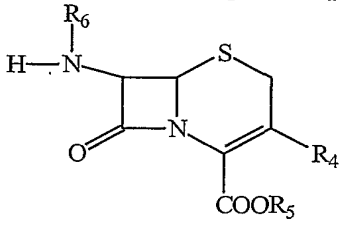




or a standard cephalosporin substituent;

R_5 is H or a salt or a carboxylic protecting group,

said process comprising the step of acylating a compound of formula **(III)**

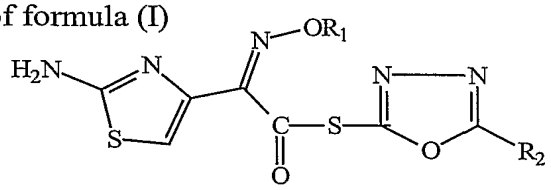


(III)

wherein, R_4 and R_5 are defined as above

R_6 is H or silyl

with a compound of formula (I)



(I)

wherein, R_1 and R_2 are as defined above.

in the presence of an organic solvent, an organic base and a silylating agent at a temperature in the range of –10°C to +30°C.

7. The process of claim 6 wherein R_5 is hydrogen or alkali metal salt.

8. The process of claim 6 wherein said compound of formula II is a syn isomer.

9. The process of claim 6 wherein R_6 is H, the acylation is performed in the presence of water and an organic solvent selected from the group consisting of tetrahydrofuran, dichloromethane, acetonitrile, acetone, N,N-dimethylacetamide, N,N-dimethylformamide, dioxane, and mixtures thereof.

10. The process of claim 6 wherein R_6 is silyl, the acylation is achieved by performing the reaction in an aprotic organic solvent like halogenated hydrocarbon, toluene, alkyl ether preferably in dichloromethane.

11. The process of claim 6 wherein the organic base is selected from the group consisting of triethylamine, diethylamine, tributylamine, N-methylmorpholine, N-methylpyridines, N-methylanilines, 1,5- diazabicyclo[4.3.0] non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.2]undec-7-ene, dimethylaminopyridine, or mixtures thereof.

12. The process of claim 6 wherein R_2 is methyl, R_4 is (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, purification of this compound is achieved by dissolving the crude product in a mixture of water and water miscible organic solvent selected from acetone, isopropyl alcohol, dioxane or mixtures thereof.

13. The process of claim 6 wherein R_2 is methyl, R_4 is (2,5-dihydro-6-hydroxy-2-methyl-5- oxo-1,2,4-triazin-3-yl)thiomethyl, the colour impurities are separated at –10°C to 0°C and precipitation by water miscible organic solvent selected from acetone, isopropyl alcohol, dioxane or mixtures thereof.

STATEMENT UNDER ARTICLE 19 (1)

The applicant has amended claims to impart additional clarity. The present claims reflect a process specifically targeted for the preparation of cephalosporin antibiotics using a novel active thioester as one of the reactants. The process provides a method for the preparation of cephalosporin antibiotics in high yield and purity, allowing commercial exploitation of the process. In addition, the process also obviates the contamination of final cephalosporin antibiotic with the side product usually encountered in the process for the preparation of cephalosporin antibiotics using novel active thioester as an acylating agent in the process. The applicant undertakes that therein no new matter has been added in claims.

INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/IN 01/00028

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 C07D501/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 806 424 A (RANBAXY LABORATORIES, LTD.) 12 November 1997 (1997-11-12) the whole document	1-13
X	US 5 869 649 A (KHANNA J G ET AL) 9 February 1999 (1999-02-09) cited in the application the whole document	1-13
X	US 4 767 852 A (ASCHER G) 30 August 1988 (1988-08-30) cited in the application the whole document	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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